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Schizophrenia: developmental disturbance of brain and mind?

MD Stefan and RM Murray

Department of Psychological Medicine, Institute of Psychiatry, London, UK

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Schizophrenia is the most severe of the mental illnesses and affects approximately 0.8% of the population in Western societies. Postmortem and neuroimaging studies show that patients with schizophrenia have slightly larger cerebral ventricles than normal and a decrease in cortical volume, most markedly in the left temporal lobe. These changes are present at diagnosis and appear to show little change over extended periods of follow-up. Associated findings such as lack of normal cerebral asymmetry and cytoarchitectonic changes suggestive of impaired migration of cortical neurons implicate aberrant neurodevelopment. Schizophrenics also show an excess of pregnancy and birth complications, and an association with prenatal exposure to maternal influenza. These and reports of abnormal psychological development in pre-schizophrenic children add further support to the theory that the disorder has neurodevelopmental origins. ☐ *Neuropathology, neuropsychology, pathogenesis, schizophrenia*

RM Murray, Department of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK

On the face of it, schizophrenia is not a promising candidate for a neurodevelopmental disorder. The diagnosis is rarely made before patients reach their late teenage years, and symptoms can arise for the first time even among the elderly. No morphological or neuropsychological correlates of sufficient specificity to be of diagnostic value have ever been reported, although a host of subtle structural abnormalities have been described. Nevertheless, the theory that schizophrenia may have its origins in abnormalities of early brain development has gained widespread acceptance. In this paper we briefly review some of the evidence behind this position and its implications for our understanding of the disorder.

Morphological abnormalities

Neuroanatomy

The search for a neuroanatomical substrate to schizophrenia has a history stretching back to the early years of the century and the postmortem studies carried out by investigators such as Southard (1). Research into the neuropathology of schizophrenia swung in and out of scientific fashion; a vast literature accumulated, but findings proved inconsistent and difficult to replicate. Corsellis noted in 1976 that "the possibility has to be faced that present histological methods are not adequate to demonstrate any convincing structural substrate for the....'functional' psychoses" (2).

This situation was transformed by developments in techniques for the quantitative assessment of postmortem material and the availability of imaging tools such as computed tomography and magnetic resonance (MR) that provided for precise evaluation of brain structure in living patients. The core finding in schizophrenia, of lateral ventricular enlargement, is now well established (3, 4, 29), but the degree of enlargement is small. Numerous other morphological abnormalities have been reported. Schizophrenic brains appear to be smaller (5), there is sulcal widening and reduced cortical volume (6), particularly in the temporal lobes (7), and many more localized abnormalities have also been described (8).

Most of these findings are non-specific and tell us little about pathogenesis, but there are some clues to the processes that might be involved. Normally rare developmental abnormalities such as agenesis of the corpus callosum, aqueduct stenosis, cavum septum pellucidum, cerebral hamartomas and arteriovenous malformations occur with increased frequency in schizophrenia (9). More subtle anomalies also point to aberrant development, e.g. Jakob and Beckmann's description (10, 11) of temporal lobe sulco-gyral abnormalities in a postmortem series of schizophrenic brains. This finding attracted a great deal of interest because the timing of gyrification in the human brain is largely intrauterine. The primary sulci become visible between ontogenic weeks 16 and 29 (12), so sulco-gyral abnormalities are suggestive of a pathological process affecting the fetal brain at this stage of development. The study was not blind, and may have paid insufficient regard to sex differences in sulco-gyral pattern (13), but similar findings were recently reported by investigators blind to diagnosis using three-dimensional surface reconstructions of MR scans in a sample of 15 male chronic schizophrenics (14). Further interest in macroscopic markers of abnormal neurodevelopment has focused on abnormalities of symmetry: e.g. failure to develop

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normal cerebral asymmetry has been reported in some postmortem (15) and MR (16, 17) studies, although these findings remain controversial (18).

At the cellular level, there have been a number of reports of abnormal cortical patterns of neuronal organization (19, 20), which in themselves could be consistent with either neurodegenerative or neurodevelopmental processes. In their original series, Jakob and Beckmann reported cytoarchitectural abnormalities in the parahippocampal cortex consistent with displacement of pre-alpha (layer II) neurons. The validity of this finding is critically dependent on accurate anatomical localization within this cytoarchitecturally variable region of cortex (21), but is echoed by reports (22, 23) of apparent displacement of nicotinamide-adenine dinucleotide phosphate-diaphorase (NADPH-d) neurons in temporal and prefrontal cortex and white matter. These cells are believed to be remnants of the cortical subplate, a transient fetal structure that may also be implicated in gyrification (12). Such neuronal displacement implicates failure of neuronal migration, a process that occurs during the second trimester of fetal development (24). Abnormal neuronal organization and neuronal disarray have been reported by other investigators in parahippocampal cortex (25) and hippocampus (26), although these data have not proved to be consistently replicable (27).

Neuronal displacement and disarray and macroscopic abnormalities of symmetry and sulco-gyral pattern are suggestive of aberrant neurodevelopment, but are not conclusive. Several findings weigh against the most likely alternative of a neurodegenerative process. The balance of evidence is that the brain abnormalities seen in schizophrenia are present at first onset (28) and are non-progressive (29). Furthermore, markers of neurodegeneration, such as proteins, associated with glial response are largely absent, although there may be a small degree of periventricular gliosis (30).

Other morphological markers

Two extracerebral markers of abnormal fetal development provide indirect support for the idea that aberrant neurodevelopment is implicated in schizophrenia. Dermatoglyphic asymmetry is thought to reflect second-trimester fetal maldevelopment and appears to be associated with schizophrenia (31). Minor physical anomalies have been reported to occur with greater frequency in schizophrenic patients compared to normal controls and to patients with bipolar affective disorder (32).

Neuropsychological abnormalities

Neuropsychological deficits in schizophrenia

The disabling cognitive deficits seen in schizophrenia include general intellectual impairment (33) as well as more circumscribed abnormalities, e.g. of memory and executive function. These are almost certainly a primary feature of the disorder. Functional neuroimaging studies hold out the promise of linking these deficits to their physiological substrates (34, 35), and Weinberger, among others, has argued that cortical disconnection and neuronal miscommunication are the likely outcome of the morphological abnormalities that have been reported (36).

"Premorbid" deficits

Evidence is growing that some neuropsychological deficits may be present before schizophrenia becomes clinically apparent. The presence of "schizoid" personality traits has long been held to be a risk factor for the later development of schizophrenia. It now appears that such traits may reflect deficits in cognition and in social behaviour that are part of the disease process itself, and that these may become apparent early in life. For example, when they viewed home movies of siblings made in the first 5 years of life, clinicians could, with some degree of reliability, pick out the child who would later receive a diagnosis of schizophrenia; the main cues appeared to be abnormalities of social behaviour (37) and of movement and posture (38).

In a study of 4746 individuals born in March 1946 in the UK, Jones and colleagues (39) found early evidence of impaired educational test performance and avoidance of social interaction in those 30 children destined to receive a diagnosis of schizophrenia in adult life. These findings are echoed in a separate study, by Done and colleagues (40), of a 1958 cohort, which intriguingly also suggests a significant sex difference, with boys worse affected. Individuals who would later be diagnosed as suffering from bipolar affective disorder did not appear to suffer such deficits. Thus, at least a subgroup of individuals who go on to develop the striking positive symptoms of schizophrenia may have been subtly impaired for many years beforehand.

From pathogenesis to aetiology

The nature and timing of the events that disrupt neurodevelopment, and those that lead from subclinical abnormalities of psychological and social function to the dramatic symptoms of acute schizophrenia, remain obscure. Some conclusions can, however, tentatively be drawn.

Genetics and molecular pathology

There seems no doubt that there is a heritable component to the aetiology of schizophrenia. It is well established that first-degree relatives have an increased risk of developing the disease, and twin studies indicate a higher level of concordance for developing schizophrenia in monozygotic (MZ) compared to dizygotic (DZ) twins (41). It is equally clear that genetic predisposition is not the whole story: concordance in MZ twins is far from absolute (about 50%), and MZ twins discordant for schizophrenia can be distinguished on the basis of ventriculomegaly and temporal cortical volume (42, 43). The predisposing genes have

yet to be identified, but increasing interest is now focusing on gene products implicated in neurodevelopment (44), some of which, such as the embryonic isoform of neural cell adhesion molecule, have been reported to be reduced in expression in patients with schizophrenia (45).

Environmental contributions

The morphological abnormalities that have been reported in schizophrenia are consistent with a neurodevelopmental event occurring in the second trimester of fetal development. This does not exclude the possibility of much later adverse environmental exposure, such as head injury or drug abuse, triggering the onset of positive psychotic symptoms. Such dual exposure may indeed account for a proportion of cases, but the more parsimonious model would suggest that the onset of frank psychotic symptoms reflects the delayed sequelae of earlier developmental aberration, which is then expressed as the brain continues to develop in adolescent and adult life. Delayed emergence of abnormal behaviour following lesions sustained during early development is a well-recognized phenomenon (9, 36), and is seen, for example, in animal models where ventral hippocampal lesions, initially "silent", are followed as the animal matures by hyperactivity and increased responsiveness to stressful stimuli and to dopamine blockade (46). The inherited neurodevelopmental disease metachromatic leucodystrophy is more likely to be associated with schizophreniform symptoms if clinical onset is in adolescence (36, 47). In this case, as in schizophrenia, late maturational events, such as myelination of prefrontal nerve tracts and perforant pathway (48), or abnormal synaptic plasticity (49, 50), may reveal earlier developmental abnormalities.

Schizophrenia is commoner among those born in the late winter and early spring, so one environmental stressor potentially affecting fetal brain development that has received considerable attention is exposure *in utero* to maternal infection in the cold winter months. There is evidence to suggest that an increase in the number of births of individuals subsequently diagnosed as schizophrenic follows influenza epidemics (51, 52). Although both the existence and the importance of this effect remain controversial (53), several studies (54, 55) indicate that the increased risk for winter births is enhanced among those born in large cities: one explanation could be the increased risk of prenatal exposure to infections such as influenza in densely populated areas.

Numerous studies have found that a history of pregnancy and birth complications is associated with schizophrenia (32). Hypoxic ischaemia in the pre- or perinatal period can lead to intraventricular or periventricular bleeds, resulting in ventricular enlargement. This might be one mechanism for ventriculomegaly in schizophrenia (56). Exocitotoxic damage associated with perinatal hypoxia could also account for some of the neurochemical abnormalities (e.g. of glutamatergic function) that are found (57). However, complications arising at around the time of birth may reflect much earlier abnormal fetal development associated with defective genetic control of neurodevelopment and adverse environmental exposure. According to one recent study, schizophrenic patients whose mothers reported second-trimester influenza had lower birthweight and were almost five times more likely to have suffered subsequent pregnancy and birth complications (58). Preschizophrenic babies have smaller head circumference than controls (59) and some studies suggest that schizophrenic patients as a group appear to be of lower birthweight than the general population (60). Further evidence supporting a significant environmental role in the pathogenesis of schizophrenia comes from a study of the Dutch population subjected to nutritional deprivation during the Second World War: an increase in the rate of schizophrenia was found among those subjected to severe malnutrition during the third trimester *in utero* (61).

Several studies have found schizophrenic males to be at greater risk of obstetric complications and of preschizophrenic behavioural abnormalities, and male schizophrenics also have more marked structural brain changes (62). This may be related to the fact that schizophrenia, tightly defined, is commoner in males. It is also of earlier onset and greater severity (63), a pattern that is also seen in other neurodevelopmental disorders.

Conclusion

The neurodevelopmental hypothesis does not implicate any one specific aetiology: multiple genetic and environmental factors may be relevant, and these may interact in a complex manner to adversely affect fetal brain development. Individuals thus affected are likely to demonstrate abnormalities in cognition and behaviour many years before more obvious symptoms emerge and a diagnosis is made. The onset of schizophrenic symptoms may be triggered by secondary exposure to adverse environmental stimuli, but is embedded within the trajectory of deviant neurodevelopment that was set in train many years before.

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